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Cardiology

RISK STRATIFICATION OF HEART FAILURE BY ISCHEMIC MITRAL REGURGITATION IN PATIENT WITH MYOCARDIAL INFARCTION

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ABSTRACT One of the important complications which causes the increase of mortality and economic burden on patient is the ischemic MR. Its main pathophysiology is the remodeling of the LV after MI which causes the hemodynamic load and heart failure. However, the data on relationship between ischemic MR and duration of heart failure is very few. We prospectively studied 300 patients who admitted for acute myocardial infarction in our hospital. All patients were assessed by echocardiography and graded MR as mild, moderate, and severe according to regurgitant jet area which is less than 20%, 20 – 40%, and more than 40% of the left atrial area, respectively. The median duration of follow up was 1 year (range 6-12 months). Mild and moderate or severe ischemic MR was present in 40.2 and 6.4% of patients respectively. The hazard ratios for HF were 2.9 (95% confidence interval (CI), 1.9–4.3; P<.001) and 3.7 (95% confidence interval (CI), 2.1-6.5; P<.001) in patients with mild and moderate or severe ischemic MR respectively, with compared to patients without ischemic MR, after adjusting for ejection fraction and other clinical variables like age, sex, Killip class, previous infarction, hypertension, diabetes mellitus, anterior wall infarction, ST elevation infarction and coronary revascularization. In patients with mild ischemic MR, the adjusted hazard ratio for death was 1.1 (95% CI 0.7-1.7; P=.42), where as in moderate or severe ischemic MR it was 2.1 (95% CI 1.3-3.5; P=.02).

KEYWORDS : xcrumb rubber, utilization, compressive strength, low cost, sustainable

INTRODUCTION

Acute coronary syndrome is an one of the most common causes for the heart failure.[1,2] Development of heart failure causes the increase in mortality in acute myocardial infarction patients, compared with other survivors of MI.

There are many factors which causes the eventual development of heart failure after acute myocardial infarction. A better understanding of these factors helps to identify the high-risk patients to develop heart failure and early implementation of preventive measures.[2] The important factors which contribute to HF after acute MI are loss of functioning myocytes, development of myocardial fibrosis, and subsequent left ventricular remodeling. The remodeling of LV causes the dilatation and neurohormonal activation, which causes for the progressive dysfunction of the remaining viable myocardium. Many studies have been given important to mechanisms that affect loading conditions as pathophysiological mechanism for progression of HF.[3-5] One of an important cause for these hemodynamic loads during this active LV remodeling is the development of the ischemic MR.

In many studies it is concluded that development of ischemic MR is an independent predictor of increased mortality following MI.[6-9] The current available data on relationship between ischemic MR and the risk for long-term development of HF is very few.[10,11]

METHODS

The study design was a prospective observational study, in which cohort enrolled all patients admitted to the intensive coronary unit with acute MI. The eligible criteria for enrollment in the study if they had a diagnosis of MI using the principle of American College of Cardiology[12], and they had survived the index event. Patients were excluded from the study with following features, which included (1) with previous history of HF, (2) patients who underwent mitral valve surgery during the index hospitalization, and (3) with organic MR. The study protocol was approved by ethical committee on human research. The primary end points of the study were (1) all- cause mortality and (2) development of HF, defined by readmission to the hospital for the management of following symptoms and signs, (1) presence of new onset dyspnea, (2) edema with one or more concurrent signs, including ventricular gallop rhythm, bilateral post tussive rales in at least the lower third of the lung fields, elevated venous pressure, or pulmonary venous congestion seen on x-ray film with interstitial or alveolar edema. After hospital discharge, clinical end point information was obtained by contacting each patient individually and reviewing the hospital course if the patient had been re- hospitalized for major clinical events.

Following admission for the index event, patient left ventricular function and presence and degree of MR was assessed by echocardiographic examination without knowledge of the patient outcome. MR was assessed from the parasternal long axis, apical 4 and 2 chamber, apical long axis, and subcostal views, and it graded by color Doppler flow mapping, jet eccentricity, and integrating jet expansion within the left atrium[8,13]. MR considered severe if the jet area was more than 40% of the left atrial area. If it between 20 – 40%, it considered as moderate, whereas if it less than 20%, considered as mild.[8,14] According to these patients were grouped to one of the following three categories: no MR or trace MR, mild ischemic MR, and moderate or severe ischemic MR.

Data are expressed as mean ± SD. The baseline characteristics and echocardiographic variables of the study groups were compared using analysis of variance, with posttest for linear trend. The linear-by-linear X^2 test was used to compare noncontinuous variables.

Using Kaplan-Meier method survival curves were constructed, and comparisons were made using the log rank test. To determine the relationship between ischemic MR severity and admission for the treatment of HF, Multivariate Cox proportional hazards modeling was used. Cox proportional hazards regression analyses were performed censoring the data to the time of recurrent infarction, as recurrent MI increases the risk for HF, which will further worsen previously existing MR, and causes the new development of new ischemic MR.

To determine the relationship between ischemic MR and mortality, again Cox proportional hazards modeling used. Clinical variables (like age, sex, smoking, Killip class at admission, previous infarction, anterior infarction, baseline serum creatinine level, use of reperfusion therapy, coronary revascularization, and history of DM and hypertension) and left ventricular ejection fraction were included in a stepwise multivariate model.

Analysis also tries to find out the possible interaction between LVEF and the severity of ischemic MR. it was assessed using a Cox proportional hazards regression model incorporating terms for the effect of ischemic MR, the effect of LVEF, and the interaction between ischemic MR and LVEF.

To evaluate the incremental additive information associated with the MR variables for the HF end point, the c statistic was used.[17] For clinical, clinical plus LVEF, and clinical plus LVEF plus MR variables, Multivariate Cox proportional hazard regression models were constructed. The discriminant accuracy of each model was quantified in terms of the c statistic, and the difference between the various models was calculated using the method described by DeLong et al.[18] Differences were considered statistically significant at the 2-sided P<.05 level. Statistical analyses were performed using SPSS software version 25.0 and MedCal version 19.5.

RESULTS

Between January 1, 2020, and June 30, 2020, 300 patients were enrolled for study after getting permission from patients. During the hospital stay at a median of 2 days (interquartile range, 1-3 days) after admission, Echocardiography was done and assessed the severity of the MR. Between the echocardiogram readers, the agreement was high (Cohen □, 0.78; 95% confidence interval [CI], 0.67-0.93). In 121 patients (40.2%) mild ischemic MR and in 19 patients (6.4%) (15 patients with moderate and 4 patients with severe) moderate or severe ischemic MR was noted. In **Table 1** the clinical characteristics of patients are given according to the severity of ischemic MR. Higher degrees of MR were more among patients with older and female, had higher level baseline serum creatinine, were more likely to have had a history of previous MI and smoking, DM, and hypertension; higher admission HR, higher Killip class, and lower LVEF.

The median duration of follow-up after hospital discharge was 12 weeks (range, 3-24 months). 36 patients (12%) were readmitted for the treatment of HF, with 27 HF events (9%) occurring without a preceding recurrent infarction during follow-up. After an episode of recurrent infarction in 9 patients admitted for HF. Among patients with no MR, mild MR, and moderate or severe MR, the incidences of recurrent infarction were 0.7%, 3.8%, and 4.3%, respectively (P=.001). During follow-up with increasing degrees of ischemic MR, Kaplan-Meier analysis showed a graded increased probability for HF.

Characteristic	**No or Trivial MR**	**Mild MR**	**Moderate or Severe MR**	***P* for trend**
Age, Mean±SD,Y	57±11	63±12	67±11	<.001
Female sex	28(17.5)	31(25.7)	7(37)	<.001
S. Cr level, mean±SD, mg/dl	0.9±0.5	1.1±0.4	1.2±0.6	<.001
Prior myocardial infarction	24(15)	31(25.6)	7(37)	<.001
Hypertension	72(45)	69(57)	14(74)	<.001
Diabetes mellitus	43(26.9)	40(33.1)	7(37)	.005
Current smoker	21(13.1)	28(23.15)	5(26.31)	<.001
Anterior infarction	77(48.15)	51(42.15)	6(31.58)	.004
Killip class on admission, Mean±SD	1.3±0.5	1.5±0.7	1.7±0.8	<.001
Ejection fraction, Mean±SD	48±11	42±13	38±12	<.001
Percutaneous revascularization	112(70)	86(71.1)	12(63.2)	.08
Medication at discharge				
Antiplatelet agents	157(98.13)	119(98.35)	17(89.48)	.12
ACE inhib or ARBs	136(85)	102(84.3)	15(79)	.83
B-Blockers	140(87.5)	98(81)	16(84.21)	.008

Table 1. Baseline patient characteristics according to MR severity

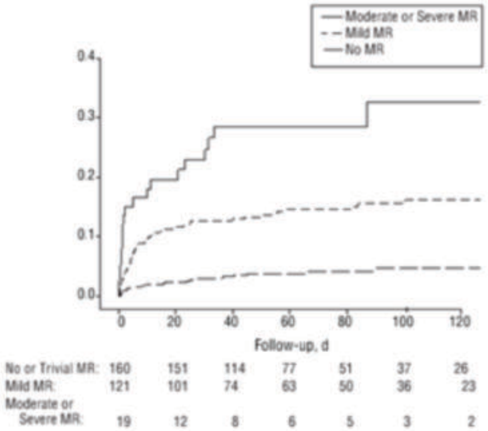

Figure 1. Kaplan-Meier plot showing the crude cumulative incidence of Admission for the treatment of heart failure according to the degree of ischemic mitral regurgitation (MR). P<.001 by log rank test for the overall comparison among the groups.

The results of the model examining the relationship between the level of ischemic MR and the risk of HF is given in **Table 2.** A graded association was noted between increasing severity of MR and risk of HF, even mild MR has risk for future HF after adjustments for LVEF and known clinical predictors of HF **(Table 2, model 1).** Other independent predictors of HF in the model included age (hazard ratio [HR], 1.2 [95% CI, 1-1.4] per 10 years; P=.001), presence of diabetes (HR, 1.6 [95% CI, 1.2-2.2]; P=.04), Killip class higher than one at admission (HR, 2.4[95% CI, 1.6-3.3]; P<.001), moderately reduced LVEF (HR, 2.5 [95% CI, 1.6-4.1]; P<.001), and severely reduced LVEF (HR, 3.6 [95% CI, 2.1-6.2]; P<.001).

When LVEF data were added to the model containing clinical variables, the c statistics increased significantly. It's (0.796±0.026) and (0.769±0.027) respectively with P=.01. Compared with the model containing LVEF and clinical variables, the model elaborated with MR data increased the overall predictive performance. It's 0.826±0.022 with P=0.02.

During follow-up as a time dependent variable, its noted that similar results were obtained after adjusting for recurrent infarction (Table 2, model 2). During the hospital course, calculated HRs for HF after excluding patients with evidence of HF (Killip class > one at admission). The adjusted HRs for HF were 2.8 (95% CI, 1.4-5.6; P=.001) and 4.7 (95% CI, 2.1-10.7; P<.001) respectively for mild and moderate or severe ischemic MR patients, using patients without MR as reference group.

MR Severity	No. of Patients	No. (%) of events	Unadjusted	Adjusted for Clinical Variables	Adjusted for LVEF and Clinical Variables
Model 1					
None or Trivial	160	5 (3.15)	1.02	1.02	1.02
Mild	121	17(14.1)	3.6(2.3-5.6)	2.8(1.7-4.3)	2.6(1.6-3.9)
Moderate or severe	19	7(36.9)	9.2(5.3-15.6)	5.2(2.9-8.1)	3.9(2.1-6.7)
Model 2					
None or Trivial	160	6(3.75)	1.02	1.02	1.02
Mild	121	21(17.35)	3.9(2.5-5.9)	2.6(1.6-4.1)	2.5(1.9-6.4)
Moderate or severe	19	8(42.1)	8.7(5.2-14.9)	4.8(2.8-8.2)	4.1(2.4-6.9)

Table 2. Unadjusted and adjusted Cox Proportional Hazards Model for Admission for Heart Failure According to Severity of MR.

11 patients (10.7%) died, during the follow-up period. The frequency of readmission among died patients for HF before death increased with higher degree of ischemic MR (16.4%, 41.1%, 48.1% in patients without, mild and moderate or severe ischemic MR, respectively; P<.001)

During follow-up with greater severity of ischemic MR, Kaplan-Meier estimates indicated an increased probability of death (Figure 2). Patients with moderate or severe MR was independently associated with an increased adjusted risk for mortality was noted in a multivariate Cox proportional hazards regression model.

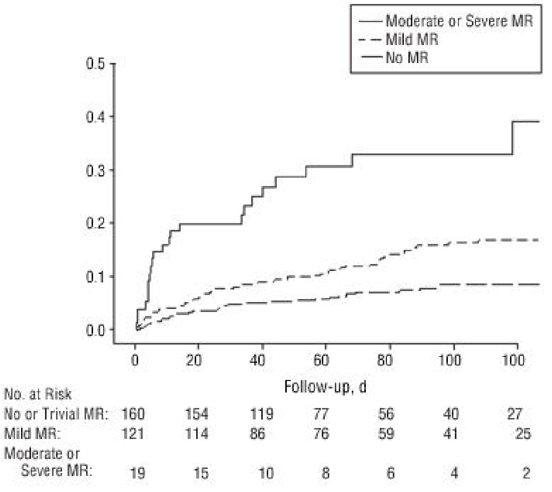

Figure 2. Kaplan-Meier plot showing the crude cumulative incidence of death according to the degree of ischemic mitral regurgitation (MR) P<.001 by log rank test for the overall comparison among the groups.

According to LVEF and degree of MR, event rates for the combined end point of HF and death are shown in Figure 3A. There was a graded increase in HF or death with decreasing LVEF, in patients without ischemic MR or with mild MR. However, event rates were high among patients with moderate or severe MR regardless of LVEF.

It was noted, in a Cox proportional hazard regression analysis, that there was a significant relationship between LVEF and moderate or severe ischemic MR in an unadjusted model containing only the main effects of LVEF and ischemic MR severity (P=.01) , where as in the adjusted model it is .03, such that the relative risk for the combined end point of HF and death was higher in patients with preserved LVEF. Therefore, the study population divided into 6 groups for subsequent analysis based on the severity of ischemic MR and the presence of preserved (≥45%) or reduced LVEF. The HR for the combined end point of HF and death in patients with moderate or severe ischemic MR compared with patients without ischemic MR was 2.4 (95% CI, 1.4-3.8), within the group of patients with reduced LVEF. Whereas it was 3.9 (95% CI, 1.7-9.2; P=.001), among patients with preserved LVEF.

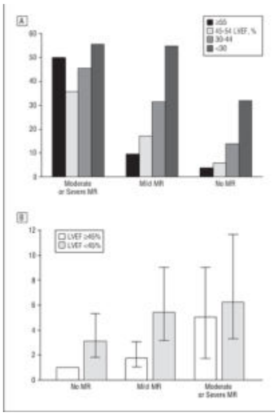

Figure 3. Interaction between the degree of ischemic mitral regurgitation and left ventricular ejection fraction. A, Event rates for the combined end point of heart failure (HF) and death according to left ventricular ejection fraction (LVEF) and the degree of ischemic mitral regurgitation (MR). B, Adjusted hazard ratios for mortality or admission for HR after hospital discharge according to LVEF (≥45% vs <45%) and the degree of ischemic MR. The reference group is patients without ischemic MR and with LVEF of at least 45%.

DISCUSSION

In the present study, we attempted to found prospectively determine the severity of ischemic MR in survivors of acute MI provided prognostic information with regard to HF and death following hospital discharge. In this study we demonstrate a graded positive association between the severity of MR and the development of HF and all-cause mortality. Compared to patients without ischemic MR, even mild ischemic MR was associated with an increase in the risk of HF. There is an independent prognostic value and incremental effect to that provided by LVEF and clinical variable for MR severity. Among low-risk patients with preserved LVEF, the effect of moderate or severe MR was particularly striking.

Compared with survivors of MI without HF, the development of HF in patients after MI causes several-fold higher risk of death.[3-5] Advanced age, DM, and reduced LVEF are the most consistent predictors of the HF after MI among several clinical features. According to our study it is demonstrated the presence and severity of ischemic MR are useful indicators to stratify the risk for HF after MI. In our study, even mild MR and patients with ischemic MR with preserved LVEF are high risk for development of HF. Therefore, to predict development of HF in patients after MI, ischemic MR is an important determinant. Furthermore, according to our data, HF is a common intermediate step that heralds death in many patients.

Previously two studies show an association between ischemic MR and HF. With greater degrees of ischemic MR, Grigioni et al[11] demonstrated an increase in the risk of HF, with relative risks of 3.6 and 4.6 in patients with effective regurgitant orifices of 1 to 19 mm^2 and at least 20 mm^2 respectively. Bursi et al[10] showed moderate or severe MR was associated with HF in patients discharged with diagnoses combatable with MI.

The results of present study indicate, as a part of routine echocardiographic evaluation, a semiquantitative assessment of MR severity provides an incremental prognostic information with regard to the risk of HF, even though the use of quantitative measurement of MR severity has been emphasized for risk of HF.[11,19] In this study, we also gave the importance of ischemic MR in patients with preserved LVEF.

Although not a consistent finding,[20] altered ventricular geometry and function after infarction causes hemodynamically significant ischemic MR, which can promote further adverse remodeling.[9] In our study, an intriguing observation was that, even the mild ischemic MR causes an incremental risk for HF, even though not easily explained. In many studies it has been postulated that, MI causes the progressive remodeling and increased load on the non-infarcted myocardium that leads to geometric abnormalities of LV causes the mild MR.[7] In some patients with mild ischemic MR may experience progressive LV remodeling and dilation, with development of HF after MI.[9]

Although the degree of MR at rest is unrelated to exercise-induced changes,[23] geometric ventricular changes caused by stress may increase the regurgitant orifice area.[19,21,22] large exercise-induced increases in the effective regurgitant orifice are associated with greater risk of HF and mortality in patients with chronic ischemic left ventricular dysfunction.[19,22] A subgroup of patients in mild resting ischemic MR with large dynamic increase in MR severity are more prone to development of HF.

Patients with mild MR are also at higher risk for HF, regardless of the mechanism underlying the association between HF and mild ischemic MR. In these patients, echocardiographic follow-up may be warranted because of ventricular distortion and dilation ay progress beyond the index event leading to worsening of ischemic MR, despite appropriate medical therapy.[24]

LV conformational changes causes the development of ischemic MR. The extent of LV geometric change is more related than severity of LV dysfunction for the severity of MR.[9,25] To our knowledge, no data are available on the outcome of patients with ischemic MR and preserved LVEF, although ischemic MR is frequently observed in patients with small MIs.[26,27] Patients with moderate or severe ischemic MR and preserved LVEF also causes for high-risk mortality and morbidity, in the present study. Patients with preserved LVEF are generally good prognosis. If these patients develop ischemic MR causes the poor prognosis.

STUDY LIMITATION

Because of ongoing ventricular remodeling, as ischemic MR is a dynamic lesion, its severity may vary over time. The severity of MR in the present study was assessed in the early postinfarction period, in contrast to previous investigations.[11] It is unknown whether progressive ventricular remodeling resulted in increasing severity of MR over time in some patients, because echocardiograms were not obtained after hospital discharge. In this study, end-systolic volume index was not available, which is one of important measures of the degree of left ventricular remodeling.

Because of technical and hemodynamic limitations, the use of color Doppler for determining MR severity is inaccurate, but is part of the routine echocardiographic examination. Therefore, in some patients it is possible that misclassification of MR severity.

CONCLUSIONS

When added ischemic MR to LVEF and clinical risks, the predictor of long-term HF and death and provides incremental prognostic information in patients with a recent acute MI. With higher degrees of MR, the risk for MR and death increases incrementally. Patients with preserved LVEF, who are apparently low-risk, ischemic MR have particularly striking effect.

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